REMARKS

The specification has been amended to include the appropriate priority information. The specification has also been amended so the trademark "GeneChip" is capitalized throughout the specification and accompanied by a generic terminology where appropriate.

Claims 1-12 were pending in this application. Applicants have canceled claim 4 without prejudice, amended claims 1, 3 and 5-11, and added new claims 13-23 to more clearly point out certain embodiments of the present invention. Applicants fully reserve the right to prosecute the canceled subject matter in one or more related applications. Upon entry of the present amendments, claims 1-3 and 5-23 will be pending in the present application.

Specifically, claim 1 has been amended to include the recitation of canceled claim 4 and part of claim 5. Support for amended claim 1 can be found in the patent application publication at, *inter alia*, paragraphs 0008 and 0009; and claims 1, 4 and 5 as originally filed. Claim 3 has been amended to recite that the DNA microarray can be a high-density oligonucleotide array. Support for amended claim 3 can be found in the patent application publication at, *inter alia*, paragraph 0027, lines 15-16. Claim 5 has been amended to delete recitation that has already been incorporated in amended claim 1. The dependency of claims 5-10 has been amended to remove improper multiple dependencies. Claim 11 has been amended to recite a method of screening a gene and estimating a function of the gene. Support for amended claim 11 can be found in the patent application publication at, *inter alia*, paragraph 0013; and claims 1 and 10 as originally filed. New claim 13 relates to a method of identifying a gene of previously unknown function as a target for drug development by using genome-wide screening and *in situ* hybridization to determine changes in the expression and localization of mRNA and/or expression sequence tags in response to an event. Support for new claim 13 can be found in the patent application publication at, *inter alia*, paragraphs 0008, 0009, 0016 and 0024; Examples 1-9; and claims 1 and 11 as originally filed. New dependent claim 14 relates to the expressing of the mRNA and/or expression sequence tags in cultured cells or tissue. Support for new claim 14 can be found in the patent application publication at, *inter alia*, paragraph 0010, lines 1-4; and claim 2 as originally filed. New dependent claim 15 relates to confirming the expression of the mRNA and/or the expression sequence tag with a DNA chip or DNA microarray such as high-density oligonucleotide array. Support for new claim 15 can be found in the patent application publication at, *inter alia*, paragraph 0010, lines 4-8; and claim 3 as originally filed. New dependent claim 16 relates to the screening of cloned genes and/or expression sequence tags. Support for new claim 16 can be found in the patent application publication at, *inter alia*,

paragraph 0012; and claim 5 as originally filed. New dependent claim 17 relates to the determination of the localization and expression of at least two types of different mRNAs and/or expression sequence tags in one type of tissue or cell in a single screening. Support for new claim 17 can be found in the patent application publication at, *inter alia*, paragraph 0014; and claim 6 as originally filed. New dependent claim 18 relates to the determination of one type of mRNA and/or expression sequence tag in at least two types of different tissues or cells in a single screening. Support for new claim 18 can be found in the patent application publication at, *inter alia*, paragraph 0015; and claim 7 as originally filed. New dependent claim 19 relates to the identification of a gene that encodes a substance effective as a drug. Support for new claim 19 can be found in the patent application publication at, *inter alia*, paragraph 0016; and claim 8 as originally filed. New dependent claim 20 relates to the identification of a gene that is related to a disease. Support for new claim 20 can be found in the patent application publication at, *inter alia*, paragraph 0017; and claim 9 as originally filed. New dependent claim 21 relates to the additional step of determining the function of the gene. Support for new claim 21 can be found in the patent application publication at, *inter alia*, paragraphs 0013 and 0018; and claim 10 as originally filed. New dependent claim 22 relates to collecting tissue or cell sample from an organism at two or more different points in time after occurrence of an event. Support for new claim 22 can be found in the patent application publication at, *inter alia*, paragraph 0019; and claim 12 as originally filed. New dependent claim 23 specifies the event as ischemia or cancer. Support for new claim 23 can be found in the patent application publication at, *inter alia*, paragraph 0011. No new matter has been added.

I. OBJECTION TO THE SPECIFICATION

The disclosure is objected to because of some informalities. Specifically, the Examiner objected to the use of the trademark "GeneChip" at paragraphs 0035, 0065, 0143, 0144, 0150, 0153 and 0160.

Applicants have amended the specification at paragraphs 0035, 0065, 0143, 0144, 0150 and 0153 so that the trademark "GeneChip" is capitalized throughout the specification and accompanied by a generic terminology where appropriate. In view of the above, the objection to the specification should be withdrawn.

In addition, Applicants respectfully submit that the trademark "GeneChip" is not used in paragraph 0160. Applicants submit that the objection to paragraph 0160 was made in

error.

II. OBJECTION TO THE CLAIMS

Claims 4-10 are objected to under 37 C.F.R. § 1.75(c) as allegedly being in improper form. Applicants have canceled claim 4 without prejudice. As such, the objection is moot with respect to claim 4 and therefore, should be withdrawn. Applicants have amended the dependency of claims 5-10 to so they are no longer in improper form. Applicants submit that new claims 14-23 properly depend on claim 13.

III. REJECTIONS OF THE CLAIMS UNDER 35 U.S.C. § 102(a)

1. The Present Invention is Novel and Nonobvious Over Nagata et al.

Claims 1 and 2 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Nagata et al. (Journal of Histochemistry and Cytochemistry, Vol. 40, No. 4, page 591, 1992, Abstract). For the following reasons, Applicants respectfully disagree.

Amended claim 1 is directed to a novel method of screening genes with unknown function using genome-wide screening and *in situ* hybridization. New claim 13 is directed more specifically to the following novel method: First, a gene having expression levels that differ before and after the occurrence of an event such as ischemia, cancer or drug administration is detected with a DNA chip or DNA microarray (*e.g.*, the high-density oligonucleotide array GENECHIP™) (see specification at, *e.g.*, paragraph 0024, lines 3-8). Second, the sequence information of the gene with changed expression levels is obtained by combining the data obtained by the DNA chip or DNA microarray with bioinformatics (see specification at, *e.g.*, paragraph 0024, lines 8-11). Third, based on the gene's sequence information, a probe is designed and prepared for *in situ* hybridization to examine how the gene is distributed (or localized) in what types of tissue or cells in an organ (see specification at, *e.g.*, paragraph 0024, lines 11-16). Genes that can be used as targets for drug development have expression levels and localization that change in response to the event (see, *e.g.*, Examples 1-9 of the specification). According to the present invention, one skilled in the relevant art can examine the function(s) of a gene using information on the distribution (or localization) of the gene in tissue(s) or cell(s), and information on changes in its expression level over time and before and after the occurrence of the event.

On the contrary, Nagata et al. describes a gene whose function is already known in the relevant art. Specifically, Nagata et al. describes the localization of acyl-CoA oxidase mRNA in hepatocytes by *in situ* hybridization method using cDNA probe, and the quantification of

the amount of acyl-CoA oxidase mRNA using ^{35}S-labeled DNA probe (see Nagata et al., lines 4-9). As described therein, acyl-CoA oxidase is known to be a rate-limiting enzyme in the fatty acid β-oxidation system of the peroxisome (see Nagata et al., lines 1-2). In their study, Nagata et al. examined the localization of the acyl-CoA oxidase in order to determine what type of liver cell contains the enzyme (Nagata et al., lines 30-32). Thus, because the gene encoding acyl-CoA oxidase was already known as well as its function, the disclosure by Nagata et al. is not directed to a method of screening to identify a gene of unknown function, as in amended claim 1.

Additionally, Nagata et al. does not teach or suggest estimating a function of the gene with previously unknown function (amended claim 11). Nagata et al. also does not teach or suggest screening genes of unknown function to identify genes whose expression and localization change in response to an event as targets for drug development (new claim 13). Nagata et al. also does not teach or suggest the use of a DNA chip or DNA microarray (amended claim 3 and new claim 15). Nagata et al. also fails to teach or suggest the studying of at least two different mRNAs and/or expression sequence tags in one screening (amended claim 6 and new claim 17) or the studying of a mRNA and/or expression sequence tag in at least two types of different tissues or cells (amended claim 7 and new claim 18). Nagata et al. further fails to teach or suggest the collection of tissue or cell samples from the organism at two or more different points in time after occurrence of an event (amended claim 12 and new claim 22). Finally, Nagata et al. is silent on the event being ischemia or cancer (new claim 26).

As such, the present invention is novel and nonobvious over Nagata et al. and the rejection based on this reference cannot stand and must be withdrawn.

2. The Present Invention is Novel and Nonobvious Over Coghlan et al.

Claims 1 and 2 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Coghlan et al. (U.S. Patent No. 5,597,692). For the following reasons, Applicants respectfully disagree.

Coghlan et al. describes a hybridization histochemistry method for determining the presence and location of a specific target mRNA population in animal or plant tissue using a labeled recombinant cDNA probe (see Coghlan et al., Abstract and column 1, lines 50-52). The method can be used to confirm and extend studies on site of known peptide biosynthesis (see Coghlan et al., column 2, lines 50-57). In particular, Coghlan et al. describes a method that is useful in the "detection of the state of activity of *specific* plant genes and the detection

of plant pathogens such as, for example, plant viruses, fungi and viroids responsible for plant diseases of economic importance." (see Coghlan et al., column 3, lines 1-6) (emphasis added). In other words, Coghlan et al. describes a method useful for examining a previously known gene. As described therein, Coghlan et al. studied mRNAs for kallikrein (see Examples 1 and 2), epidermal growth factor (EGF) (see Example 3), beta hemoglobin (see Example 4), calcitonin (see Example 5), arginine-vasopressin (AVP)-neurophysin (see Example 6), and oxytocin-neurophysin I and AVP-neurophysin II (see Example 7), the sequence and activities of all of which were already known. In contrast, the claimed method relates to the identification of a gene of unknown function.

Additionally, Coghlan et al. does not teach or suggest estimating a function of the gene with previously unknown function (amended claim 11). Coghlan et al. also does not teach or suggest screening genes of unknown function to identify genes whose expression and localization change in response to an event as targets for drug development (new claim 13). Coghlan et al. also does not teach or suggest the use of a DNA chip or DNA microarray (amended claim 3 and new claim 15). Coghlan et al. also fails to teach or suggest the studying of at least two different mRNAs and/or expression sequence tags in one screening (amended claim 6 and new claim 17) or the studying of a mRNA and/or expression sequence tag in at least two types of different tissues or cells (amended claim 7 and new claim 18). Coghlan et al. further fails to teach or suggest the collection of tissue or cell samples from the organism at two or more different points in time after occurrence of an event (amended claim 12 and new claim 22). Finally, Coghlan et al. is silent on the event being ischemia or cancer (new claim 26).

As such, the present invention is novel and nonobvious over Coghlan et al. and the rejection based on this reference cannot stand and must be withdrawn.

3. The Present Invention is Novel and Nonobvious Over Toran-Allerand

Claims 1, 2, 11 and 12 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Toran-Allerand (U.S. Patent No. 5,990,078). For the following reasons, Applicants respectfully disagree.

Toran-Allerand describes a method of increasing the level of estrogen receptors in the neural tissue of a subject (see Toran-Allerand, Abstract and claims 1 and 7). Toran-Allerand describes the use of *in situ* hybridization histochemistry to identify estrogen receptor mRNA in PC12 cells both before and after long-term exposure to nerve growth factor (NGF) (see Tran-Allerand, column 13, lines 27-32). Again, the hybridization product described in

Toran-Allerand is estrogen receptor mRNA, whose sequence and function are already known. In contrast, the claimed method relates to the identification of a gene of unknown function.

Additionally, Toran-Allerand does not teach or suggest estimating a function of the gene with previously unknown function (amended claim 11). Toran-Allerand also does not teach or suggest screening genes of unknown function to identify genes whose expression and localization change in response to an event as targets for drug development (new claim 13). Toran-Allerand also does not teach or suggest the use of a DNA chip or DNA microarray (amended claim 3 and new claim 15). Toran-Allerand also fails to teach or suggest the studying of at least two different mRNAs and/or expression sequence tags in one screening (amended claim 6 and new claim 17) or the studying of a mRNA and/or expression sequence tag in at least two types of different tissues or cells (amended claim 7 and new claim 18). Toran-Allerand further fails to teach or suggest the collection of tissue or cell samples from the organism at two or more different points in time after occurrence of an event (amended claim 12 and new claim 22). Finally, Toran-Allerand is silent on the event being ischemia or cancer (new claim 26).

As such, the present invention is novel and nonobvious over Toran-Allerand. and the rejection based on this reference cannot stand and must be withdrawn.

In view of the foregoing, Applicants respectfully request that the rejections of the claims under 35 U.S.C. § 102(b) be withdrawn.

IV. REJECTION OF THE CLAIMS UNDER 35 U.S.C. § 102(e)

Claims 1 and 3 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Joly et al. (U.S. Patent No. 6,342,495). For the following reasons, Applicants respectfully disagree.

Joly et al. describes the use of agonists and antagonists of peripheral-type benzodiazepine receptors in the diagnosis and treatment of cardiac hypertrophy and other circulatory conditions (see Joly et al., Abstract and claims 1, 17, 21, 33 and 37). Joly et al. describes the use of *in situ* hybridization histochemistry to examine CVB3 viral RNA localization using digoxigenin-labeled, CVB3 strand-specific riboprobes (see column 20, lines 52-63), and the use of microarray analysis for assessment of differentially expressed genes that encode 1-8U, prostacyclin-stimulating factor, osf-2, tissue specific mRNA, insulin-like growth factor binding protein 6, OSF-1, gas-1, YMP, BTG2, pre-B cell stimulating factor homolog (SDF1a), peripheral-type benzodiazepine receptor (PTBR), and cellular ligand of annexin II (p11) (see column 6, lines 13-25, and column 20 line 66 to column 21, line 3), the

sequence and activities of all of which were already known. In contrast, the claimed method relates to the identification of a gene of unknown function.

Additionally, Joly et al. does not teach or suggest estimating a function of the gene with previously unknown function (amended claim 11). Joly et al. also does not teach or suggest screening genes of unknown function to identify genes whose expression and localization change in response to an event as targets for drug development (new claim 13). Joly et al. also fails to teach or suggest the studying of at least two different mRNAs and/or expression sequence tags in one screening (amended claim 6 and new claim 17) or the studying of a mRNA and/or expression sequence tag in at least two types of different tissues or cells (amended claim 7 and new claim 18). Joly et al. further fails to teach or suggest the collection of tissue or cell samples from the organism at two or more different points in time after occurrence of an event (amended claim 12 and new claim 22). Finally, Joly et al. is silent on the event being ischemia or cancer (new claim 26).

As such, the present invention is novel and nonobvious over Joly et al. Therefore, Applicants respectfully request that the rejection of the claims under 35 U.S.C. § 102(e) be withdrawn.

V. THE REJECTION OF THE CLAIMS UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

Claim 3 is rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ness et al. (U.S. Patent No. 6,027,890). Specifically, the Examiner alleges that in view of the teachings of Ness et al., it would be obvious to one of ordinary skill in the art that *in situ* hybridization techniques followed by DNA microarray analysis or vice versa could be utilized to investigate mRNA expression and localization with a reasonable expectation of success. For the following reasons, Applicants respectfully disagree.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. In re Jones, 21 U.S.P.Q.2d 1941, 1943-1944 (Fed. Cir. 1992); In re Fine, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988). Second, there must be a reasonable expectation of success. In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988). Third, the prior art references must teach or suggest all the claim limitations. Litton Indus. Products, Inc. v. Solid State Systems, 755 F.2d 158, 164 (Fed. Cir. 1985). The teaching or suggestion to make the claimed combination and reasonable expectation of success must both be found in the

prior art, and not based on applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Finally, the Federal Circuit has made very clear that "[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." In re Fine, 5 USPQ2d at 1600.

Applicants submit that the claimed invention is nonobvious over Ness et al., which describes the use of specialized tags and linkers to enhance sensitivity of the analysis of a wide variety of biological-based assays (see Ness et al., Abstract and column 1, lines 17-22). There is no suggestion or motivation in Ness et al. to modify the techniques or to combine the techniques. On one hand, Ness et al. generically describes *in situ* hybridization as a technique that can be used to examine the precise location of a given mRNA in a specific population of cells within a tissue by using a probe which hybridizes specifically with mRNA (see column 42, lines 33-53, and column 49, line 60 to column 50, line 5). On the other hand, Ness et al. generically describes DNA array technology as another technique that can be utilized in the identification of individual clones and to quantitatively measure the relative expression of genes in two different RNA samples (see column 54, lines 5-47).

Contrary to the Examiner's allegation that Ness et al. teaches that the techniques "may be use along or in conjunction with one another to investigate the structure or expression of a gene or its mRNA in unknown pool of nucleic acids" (see Office Action, page 5, ¶11, lines 4-6), Ness et al. teaches away from the current invention. The Examiner's attention is respectfully directed to column 41, lines 4-10 of Ness et al., which states:

> As noted above, the present invention also provides a wide variety of methods wherein the above-described cleavable tags and/or linkers may be utilized in place of traditional labels (e.g., radioactive, fluorescent, or enzymatic), in order [to] enhance specificity, sensitivity, or number of samples that may be simultaneously analyzed, *within a given method.* (emphasis added).

Not only is the Examiner's allegation unsupported (*i.e.*, the Examiner fails to point to any specific part of Ness et al. that supports the allegation that one or more nucleic acid assays may be combined), the Examiner's allegation is exact opposite to the teaching of Ness et al. Ness et al. does not teach or suggest that different nucleic acid assays can be combined. Instead, the different nucleic acid assays that Ness et al. describes are examples of how the specialized tags and linkers can be used.

In situ hybridization and DNA microarray are two different types of nucleic acid assays and relate to different purposes, *i.e.*, one relating to the examination of the localization

of genes (*in situ* hybridization), and the other relating to the examination of the expression of genes (DNA microarray). Applicant submits that one skilled in the art of gene expression would have no motivation to modify or combine the techniques of DNA microarray with *in situ* hybridization. Likewise, one skilled in the art of gene localization would have no motivation to modify or combine the techniques of *in situ* hybridization with DNA microarray.

Even assuming *arguendo* that the *in situ* hybridization technique and DNA microarray technique can be can be modified or combined, Applicants submit that there is no reasonable expectation of success offered by Ness et al. to formulate the claimed methods. As discussed above, Ness et al. relates to the use of specialized tags and linkers to enhance sensitivity of the analysis *within one assay*. Since the objective of Ness et al. is to enhance the performance of *each* one of the wide variety of biological-based assays, and not to combine the assays, the skilled artisan would not expect that one nucleic acid assay could successfully be used in combination with another nucleic acid assay. Therefore, because Ness et al. teaches away from combining assays, one skilled in the art would have no reasonable expectation of arriving at the claimed invention.

In addition, Ness et al. does not teach or suggest each and every claim limitation. First, Ness et al. fails to teach or suggest the use of *in situ* hybridization together with DNA microarray to estimate a function of a gene with previously unknown function (amended claim 1). Second, Ness et al. fails to teach or suggest screening genes of unknown function to identify genes whose expression and localization change in response to an event as targets for drug development (new claim 13). Third, Ness et al. fails to teach or suggest the examination of the expression and localization of genes both before and after the occurrence of an event (new claim 13(b)). Fourth, Ness et al. fails to teach or suggest that the expression and localization of genes change in response to the event (new claim 13(b), (f) and (g)). Fifth, Ness et al. fails to teach or suggest that the genes screened are those with unknown function (new claim 13). Fifth, Ness et al. fails to teach or suggest the *in vitro* expression of mRNA and/or expression sequence tag (original claim 2 and new claim 14). Sixth, Ness et al. fails to teach or suggest the studying of at least two different mRNA and/or expression sequence tag in one screening (amended claim 6 and new claim 17) or the studying of a mRNA and/or expression sequence tag in at least two types of different tissue or cell (amended claim 7 and new claim 18). Seventh, Ness et al. fails to teach or suggest the collection of tissue or cell sample from the organism at at least two different points in time after occurrence of an event (amended claim 12 and new claim 22). Finally, Ness et al. fails to teach or suggest the event

as being ischemia (new claim 26). Accordingly, even in combination, Nell et al.'s generic description on *in situ* hybridization and DNA microarray do not teach or suggest all claim limitations.

Finally, the Examiner has improperly used hindsight reconstruction to pick and choose among isolated disclosures in Ness et al. to reconstruct the claimed invention. Such hindsight, however, is improper. Applicants respectfully submit that *hindsight reconstruction* has been used in the rejection of the present invention to combine one nucleic acid assay with another nucleic acid assay with different use. Applicants submit that any rejection of the instant claims under Section 103(a) based on Ness et al. would indicate the improper use of hindsight gained from Applicants' own specification. Hindsight should be avoided in applying the nonobviousness requirement. *Panduit Corp. v. Dennison Mfg. Co.,* 810 F.2d 1561, 1 U.S.P.Q.2d 1593 (Fed. Cir. 1987), *cert. denied,* 481 U.S. 1052 (1987).

As such, Applicants respectfully request that the claim rejections under 35 U.S.C. § 103(a) be withdrawn.

VI. THE PRESENT INVENTION IS NOVEL AND NONOBVIOUS OVER SCHENA ET AL.

The Office Action indicates that Schena et al. (Science, Vol. 270, pages 467-470, October 20, 1995) is prior art and pertinent to Applicants' disclosure. Schena et al. describes monitoring of gene expression patterns with DNA microarray but does not teach or suggest the combination of DNA microarray and *in situ* hybridization. Schena et al. is also silent about screening of genes with changes in expression level before and after occurrence of an event, as well as the identification of genes with unknown functions. Hence, the presently claimed invention is patentable over this reference.

VII. INFORMATION DISCLOSURE STATEMENT

Applicants submit concurrently herewith an Information Disclosure Statement listing references C01-C03. Consideration and entry of the references are respectfully requested.

CONCLUSION

In light of the submissions herewith, the above remarks and amendments, it is submitted that all outstanding objections and rejections have been overcome. Attorneys for Applicants respectfully submit that the newly added claims fully meet all statutory requirements for patentability. Withdrawal of the rejections and allowance of claims 13-23 are respectfully requested. Should the Examiner not agree with Applicants' position, then a telephonic interview is respectfully requested to discuss any remaining issues and expedite the eventual allowance of the application.

Respectfully submitted,

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Enclosures